ELSEVIER

International Journal of Antimicrobial Agents 16 (2000) 123–125

INTERNATIONAL JOURNAL OF
Antimicrobial Agents

www.ischemo.org

Antibacterial prophylaxis

Mario Cruciani *

Department of Infectious Diseases, University of Verona, Ospedale Civile Maggiore, P.le Stefani, 1-37126 Verona, Italy

Abstract

Bacterial infections remain an important cause of morbidity and mortality in neutropenic patients. A number of prophylactic strategies have been used in order to reduce the risk of infection during severe granulocytopenia. The measures that have been investigated include isolation of the patient, granulocyte transfusion, active or passive immunisation, acceleration of granulocyte recovery and prophylactic use of antibacterial agents. However, many of these approaches have fallen out of favour, mostly because of concerns about the long lasting efficacy. This paper focuses on the available prophylactic strategies, with emphasis on the use of antibacterial agents. © 2000 Elsevier Science B.V. and International Society of Chemotherapy. All rights reserved.

Keywords: Neutropenic patients; Granulocytopenia; Bacterial infections

During the last few years, considerable improvement has been made in the management of infections in neutropenic patients. Nonetheless, bacterial infections remain an important cause of morbidity and mortality in neutropenic cancer patients, particularly after the introduction of more aggressive anti-neoplastic chemotherapeutic regimens. Fever is usually a is common problem in most neutropenic patients, and about one third of them have a microbiological documented infection, primarily bacteremia [1].

Stemming from the concept of susceptibility to infections, a number of interventions have been put into clinical practice in order to reduce the risk of infection during severe granulocytopenia. The measures that have been used include isolation of the patient, granulocyte transfusions, active or passive immunisation, acceleration of granulocyte recovery with lithium or recombinant colony-stimulating factors, and the use of prophylactic antimicrobial agents [2,3]. Many of these approaches have fallen out of favour, mostly because of concerns about their long lasting efficacy. The use of antibacterial agents, however, continues to stimulate interest, as a potentially effective measure for prophylaxis in granulocytopenic patients (Table 1).

1. The evolution of antibacterial prophylaxis for neutropenic patients

Since most infections in neutropenic patients may originate from the microflora that colonise the skin and mucosal surfaces, suppression of endogenous organisms from these body sites should protect the host against infections. This can be achieved by administering antimicrobials that would selectively target these potentially pathogenic organisms leaving intact the anaerobic flora responsible for colonisation resistance of the digestive tract [4].

Early studies with oral non-adsorbable antibiotics (ONA) have shown reduction in infection rates in granulocytopenic patients. Regimens with ONA however, are poorly tolerated, making compliance a problem [5]. Failure to take ONA has resulted in rapid gut re-population with potentially pathogenic organisms and consequent infection. The use of ONA has also been associated with colonisation by resistant gram-negative strains.

A large number of clinical trials have been conducted to evaluate the efficacy of prophylactic trimethoprim–suphamethoxazole (TMP/SMX) in granulocytopenic patients. Despite the fact that most of the earlier studies suggested benefit from TMP/SMX prophylaxis, a number of additional trials have led to negative results. Resistance turned out to be an important problem when using TMP/SMX. In a large EORTC study, the

* Fax: +39-45-8343933.
E-mail address: maow@virgilio.it (M. Cruciani).

PII: S0924-8579(00)00216-8

Table 1
Antibacterial prophylaxis

Past	Present	Future
Active or passive immunisation	Identification of patients in whom benefit of prophylaxis is maximised	Better understanding of the pathogenesis of febrile episodes
Leukocyte transfusions	Reduction in the amount and duration of antibiotic therapy according to the administered prophylaxis	Better technology for prophylactic granulocyte transfusions
Acceleration of neutrophil recovery (lithium)	Acceleration of neutrophil recovery (G-CSF, GM-CSF)	Cost-effectiveness and cost-benefit analysis of prophylactic strategies
Reverse isolation, LAF		Antibiotic-lock technique for prevention of CVC-related infections
Oral non absorbable antibiotics; TMP/SMX	Fluoroquinolones ± anti-gram-positive agents	New antimicrobial agents (quinolones with enhanced activity against gram-positive?)
		Bone marrow protective agents (i.e. amifostine)

rate of blood isolates resistant to TMP/SMX was significantly higher in TMP/SMX recipients in comparison with 'placebo' recipients (80 vs. 26%, respectively) [6].

Fluoroquinolones are now widely used as prophylaxis for bacterial infections in neutropenic patients. After more than 10 years of clinical use, a reassessment of quinolone prophylaxis is necessary. The aims of successful prophylaxis in neutropenic patients should include a reduction in the risk of developing specific infections and a reduction in infection related mortality, a reduction in the number of episodes of febrile neutropenia, and a decrease in the empirical use of antibiotics for febrile episodes [2,7]. Several studies have clearly shown that fluoroquinolones significantly reduce the occurrence of gram-negative bacterial infections [8]. When quinolone are used as prophylaxis, the rate of gram-negative bacteremia is reduced to 1–2% [1]. In contrast, the benefits of fluoroquinolone prophylaxis on other parameters of infection-related morbidity such as the occurrence of gram-positive infection and fever, the need for systemic antibiotics, and the occurrence of infection-related mortality are not evident.

The use of survival as the outcome variable in the neutropenic patient poses particular problems. Firstly, it is often difficult to assess a specific cause of death in this population. The substantial progress made in the management of fever and neutropenia has resulted in a remarkable decrease of mortality rate, thus rendering any further improvement impractical to detect, unless several thousands of patients could be studied.

Fever is also a cloudy end-point for the evaluation of prophylactic strategies. The cause of fever cannot be identified in a large number of neutropenic patients. Analysis of clinical trials had shown that quinolones did not significantly reduce the occurrence of febrile morbidity, although a slight benefit for patients treated with these drugs had been observed (Fig. 1).

This lack of a clear correlation between the reduction of specific infections and the overall febrile morbidity has been ascribed to the possibility of a conversion from microbiologically documented infections to unexplained episodes of fever in fluoroquinolones recipients [2,7]. This hypothesis has been corroborated in a recent prospective study showing that the reduction of microbiologically documented infections among ofloxacin and ofloxacin + rifampin recipients was offset by concomitant increase in the number of episodes of unexplained fever in the study population [9]. There is some evidence suggesting that unexplained episodes of fever in granulocytopenic patients receiving fluoroquinolones can be safely managed with strategies which would allow an early discontinuation of parenteral antibacterial therapy or a reduction in the amount of antibiotic therapy directed towards gram-negative organisms [10,11].

Results of trials in which quinolones were compared with TMP/SMX, ONA or placebo showed that quinolones are not effective in preventing gram-positive infections. Prophylactic strategies combining gram-positive targeting agents (macrolides, penicillins, rifampin or vancomycin) and fluoroquinolones have generally shown a reduction in the incidence of gram-positive infections, especially that due to streptococcal species [8].

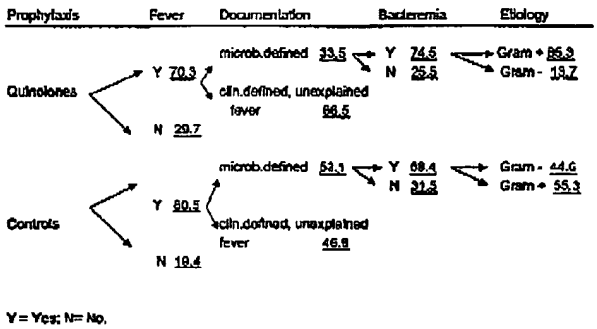

Fig. 1. Infection documentation (%) in fluoroquinolone recipient and controls (placebo, ONA, TMP/SMX). Data based on a meta-analysis of clinical trials [8].

Currently, the principal drawback to fluoroquinolones prophylaxis is represented by the emergence of resistance strains. Recent reports of fluoroquinolone-resistant *Escherichia coli* causing bacteremia among cancer patients is a matter of concern. Indeed, the emergence of such resistance will likely undermine the well recognised efficacy of fluoroquinolones in the prevention of gram-negative infections in neutropenic patients.

2. Conclusions and perspectives

The use of simple infection-control measures, such as handwashing, is probably the most cost-effective procedure for prophylaxis of infections in neutropenic patients. Despite important advances in preventive measures, catheter-related infection remains a significant problem in neutropenic patients. There is limited evidence suggesting that local administration of solution containing heparin and vancomycin by an antibiotic-lock technique is effective in preventing catheter hub colonisation with gram-positive bacteria and subsequent bacteremia during chemotherapy-induced neutropenia [12].

Since clinical benefits of prophylaxis with colony stimulating factors have not been reported universally, we need additional clinical studies and, in view of the high costs of these agents, prospective pharmacoeconomic evaluations of their use in this setting.

Other potentially useful strategies for preventing bacterial infections in neutropenic patients are summarised in the Table. Since prophylaxis with fluoroquinolones has, until now, led to a remarkable reduction in the occurrence of gram-negative infections during neutropenia in many centres, generalised statements against its use would appear inappropriate. Rather, the potential disadvantages of quinolone prophylaxis should be weighed against the benefits for each patient. More accurate and specific information on these aspects could be provided by studies incorporating cost-effectiveness and cost-benefit analysis of data.

References

[1] Klastersky J. Science and pragmatism in the treatment and prevention of neutropenic infection. J Antimicrob Chemother 1998;41(Suppl. 7):13–24.

[2] Pizzo PA. Considerations for the prevention of infectious complications in patient with cancer. Rev Infect Dis 1989;11:S1551–63.

[3] Zinner SH. Treatment and prevention of infections in immunocompromised hosts. In: Gorbach SL, Bartlett JG, Blacklow NR, editors. Infectious Diseases, second ed. Philadelphia: W.B. Saunders Company, 1998.

[4] Van der Waaij D, Berghuis-de Vries JM, Lekkerker-van der Wees JEC. Colonization resistance of the digestive tract in conventional and antibiotic-treated mice. J Hygiene 1971;69:405–11.

[5] Kerr KG. The prophylaxis of bacterial infections in neutropenic patients. J Antimicrob Chemother 1999;44:587–91.

[6] EORTC International Antimicrobial Therapy Project Group. Cotrimoxazole in the prevention of infection in neutropenic patients. J Infect Dis 1984;150:372–9.

[7] Bow EJ, Ronald AR. Antibacterial chemoprophylaxis in neutropenic patients — where do we go from here? Clin Infect Dis 1993;17:333–7.

[8] Cruciani M, Rampazzo R, Malena M, Lazzarini L, Todeschini G, Messori A, Conciq E. Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. Clin Infect Dis 1996;23:795–805.

[9] Bow EJ, Mandell LA, Louie TJ, Feld R, Palmer M, Zee B, Pater J. Quinolone-based antibacterial chemoprophylaxis in neutropenic patients: effect of augmented gram-positive activity on infectious morbidity. Ann Intern Med 1996;125:183–90.

[10] Bow EJ, Loewen R, Vaughan D. Reduced requirement for antibiotic therapy targeting gram-negative organisms in febrile, neutropenic patients with cancer who are receiving antibacterial prophylaxis with oral quinolones. Clin Infect Dis 1995;20:907–12.

[11] de Marie S, van den Broek PJ, Willemze R, van Furth R. Strategy for antibiotic therapy in febrile neutropenic patients on selective antibiotic decontamination. Eur J Clin Microbiol Infect Dis 1993;12:897–906.

[12] Carratala J, Niubo J, Fernandez-Sevilla A, Juve E, Castellsssagne X, Berlange J, Linares J, Gudiol F. Randomized double-blind trial of an antibiotic-lock technique for prevention of gram-positive central venous catheter-related infection in neutropenic patients with cancer. Antimicrob Agents Chemother 1999;43:2200–4.